

CIMBA Mutation Classification guidelines (May 2016)

Only carriers with clearly pathogenic BRCA1 or BRCA2 mutations are eligible for inclusion in CIMBA.

Types of pathogenic BRCA1/2 mutations

1. Mutations generating a premature termination codon (PTC) (except variants generating a PTC in exon 27 at or after codon 3310. Note there is a “grey zone” [codons 3310 -3325] where the pathogenicity of variants is considered to be unknown (currently excluded from CIMBA). Variants which truncate after codon 3326 are currently considered neutral and also excluded from CIMBA.)

This includes:

- ✓ small deletions and insertions
- ✓ nonsense mutations
- ✓ splice site mutations affecting -1, -2 or +1, +2 intronic nucleotide positions (except where there is contrary evidence to indicate the variant is NOT pathogenic eg. BRCA1 IVS9-2A>C (c.594-2A>C))
- ✓ other splice site mutations confirmed by *in vitro* functional studies to cause aberrant splicing leading only to, or predominantly to transcripts with a premature stop codon. If these functional studies are published, a citation should be provided.
- ✓ large genomic rearrangements

2. Large in-frame deletions or insertions that span one or more exons including:

- ✓ splice site mutations affecting -1, -2 or +1, +2 intronic nucleotide positions (except where there is contrary evidence to indicate the variant is NOT pathogenic eg. BRCA1 IVS9-2A>C (c.594-2A>C))
- ✓ other splice site mutations confirmed by *in vitro* functional studies to cause aberrant splicing leading only to, or predominantly to transcripts with a large in-frame deletion. If these functional studies are published, a citation should be provided.
- ✓ large genomic rearrangements

3. Deletion of transcription regulatory regions (promoter and/or first exon) expected to cause lack of expression of mutant allele. When available, data on allele differential expression confirming the absence of mutant transcript (citation if data are published) should be supplied.

4. Missense variants considered pathogenic by the BIC committee and/or already published variants classified as pathogenic using multifactorial likelihood approaches (e.g. Goldgar et al. Am J Hum Genet. 2004, 75(4):535-44; Chenevix-Trench et al. Cancer Res. 2006, 66(4):2019-27).

5. Mutations which do not meet the above criteria but which have been classified as pathogenic by Myriad can be included in CIMBA. They will be annotated accordingly to allow analysts to exclude them from the dataset if required.